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(54) Process and intermediates for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2"- (2"-methoxy-phenoxy)-ethyl]-amino]-propan-2-ol[carvedilol]

(57) A subject matter of the invention is a process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2"-<methoxy>-phenoxy)-ethyl]-amino]-propan-2-ol as well as the R or S enantiomer thereof and mixtures of the enantiomers and acid addition salts of these compounds, in which

4-(hydroxy)-9H-carbazole and the thus formed 1-[N-[benzyl]-2"-<methoxy>-phenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol [benzyl-carvedilol] is debenzylated by catalytic hydrogenation

a) 4-(oxiranylmethoxy)-9H-carbazole or the R or S enantiomer thereof is reacted with N-[2-(2'-<methoxy>-phenoxy)-ethyl]-benzylamine in a protic organic solvent, and the thus formed 1-[N-[benzyl]-2"-<methoxy>-phenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol [benzyl-carvedilol] is debenzylated by catalytic hydrogenation or

b) the N-[2-(2'-<methoxy>-phenoxy)-ethyl]-benzylamine is reacted with epichlorohydrin, the thus formed 1-[N-[benzyl]-2"-<methoxy>-phenoxy)-ethyl]-amino]-3-[chloro]-propan-2-ol is reacted with

Description

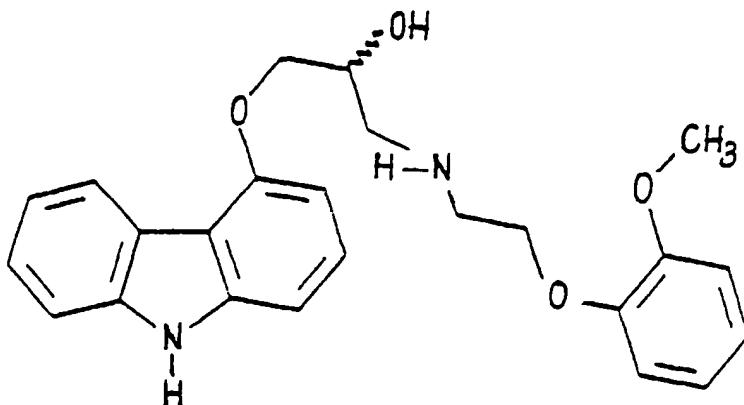
[0001] The present invention is concerned with a new process and new intermediates for preparing 1-[9H-carbazol-4'-yloxy]-3-[2''-(2''-(methoxy)phenoxy)-ethyl]-amino]-propan-2-ol [carvedilol] of formula

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as well as the optically active R or S enantiomer thereof and mixtures of the enantiomers and acid addition salts of these compounds.

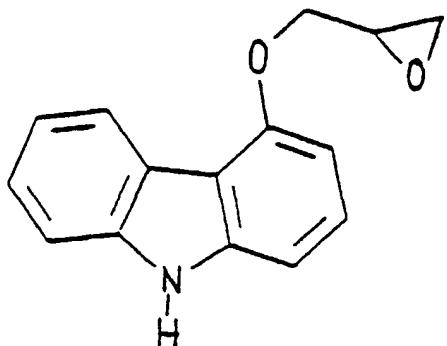
25 [0002] This compound is known under the INN name carvedilol and is used as a drug having antihypertensive, beta-adrenergic blocking and vasodilating activity. The chemical name thereof is as beforeaid, 1-[9H-carbazol-4'-yloxy]-3-[2''-(2''-(methoxy)phenoxy)-ethyl]-amino]-propan-2-ol.

[0003] The preparation of 1-[9H-carbazol-4'-yloxy]-3-[2''-(2''-(methoxy)phenoxy)-ethyl]-amino]-propan-2-ol [carvedilol] has been known from DE-OS No. 28 15 926, while the preparation of the R and S enantiomers has been 30 described in DE-OS No. 33 19 027. According to the known process, 4-(oxiranylmethoxy)-9H-carbazole of formula

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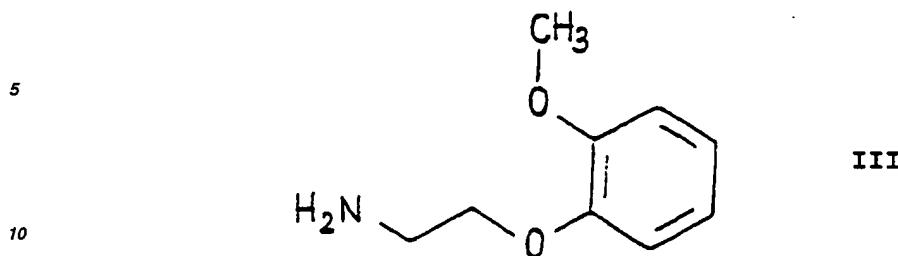


II

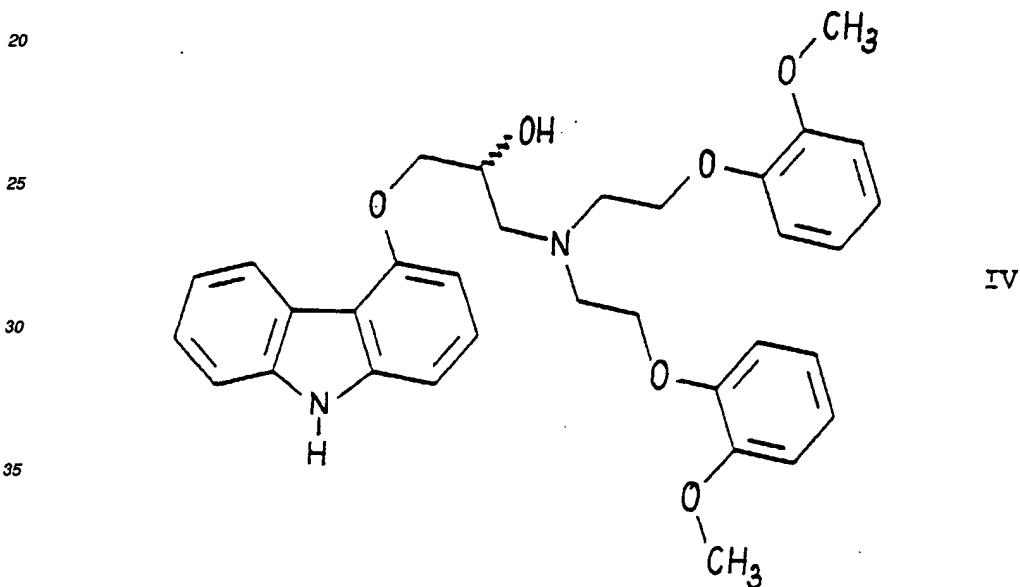
or the R or S enantiomer thereof is reacted with 2-(2'-(methoxy)phenoxy)-ethylamine of formula

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15 to produce the compound 1-[9'H-carbazol-4'-yloxy]-3-[(2''-(methoxy)phenoxy)-ethyl]-amino]-propan-2-ol [carvedilol] of formula I in a yield of 39 to 42%. The drawback of the known process consists in the fact that parallel with the formation of 1-[9'H-carbazol-4'-yloxy]-3-[(2''-(methoxy)phenoxy)-ethyl]-amino]-propan-2-ol [carvedilol] also a bis compound of formula



40 forms through the reaction of 2 molar equivalents of 4-(oxiranylmethoxy)-9-H-carbazole of formula II and 1 molar equivalent of 2-[2'-(methoxy)phenoxy]-ethylamine of formula III. This side-reaction can never be avoided, and the bis compound of formula IV is formed in an amount that is commensurable with that of 1-[9'H-carbazol-4'-yloxy]-3-[(2''-(methoxy)phenoxy)-ethyl]-amino]-propan-2-ol [carvedilol]. Consequently, the known process is uneconomical.

45 [0004] Also further possibilities for the preparation of [carvedilol] have been described in DE-OS No. 28 15 926. According to these processes, 4-[3'-(amino)-2'-(hydroxy)-propoxy]-9H-carbazole can be reacted with

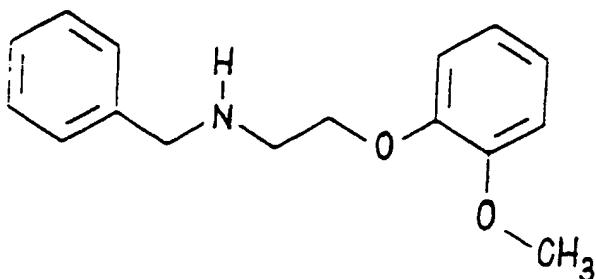
- a) 2-[2'-(methoxy)phenoxy]-ethylhalide or -sulfonate;
- 50 b) 2-[2'-(methoxy)phenoxy]-acetaldehyde followed by catalytic hydrogenation;
- c) 2-[2'-(methoxy)phenoxy]-acetylchloride, followed by reducing the formed acid amide with a complex metal hydride.

55 [0005] None of the processes a) to c) is suitable for the economical preparation of 1-[9'H-carbazol-4'-yloxy]-3-[(2''-(methoxy)phenoxy)-ethyl]-amino]-propan-2-ol [carvedilol]. In case of each process, a purification step by column chromatography is required for the separation of the product, and the preparation of the starting compound is uneconomical. In process a), the bis compound of formula IV forms, too. In case of process b), a yield of 41%, while in case of process

c), a yield of 24% can be obtained, at the most. In process c), the use of a complex metal hydride, practically lithium aluminium hydride, is also a drawback since this reaction is accompanied by an enhanced fire hazard. The latter reaction requires absolute conditions, i.e. even traces of water should be avoided.

[0006] In principle, the formation of the bis compound of formula IV can be avoided by using, instead of the primary amine 2-[2'-(methoxy)-phenoxy]-ethylamine of formula III, a secondary amine which is a derivate of the primary amine 2-[2'-(methoxy)-phenoxy]-ethylamine of formula III containing a protective group. Such a secondary amine is, for example, the N-[2-(2'-(methoxy)-phenoxy)-ethyl]-benzylamine of formula

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V.

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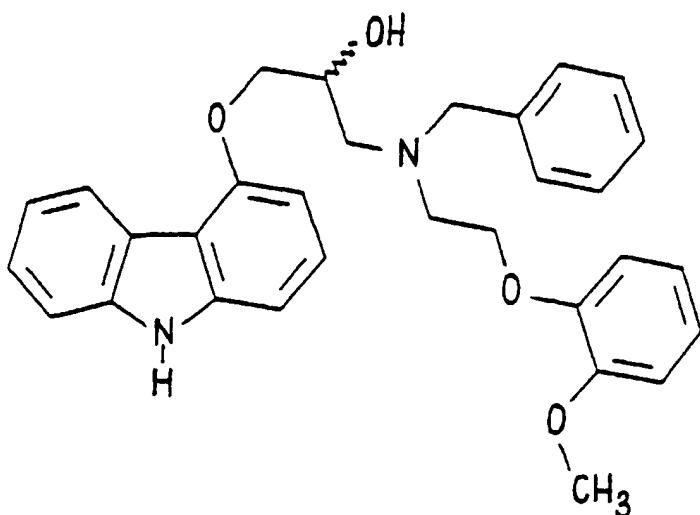
In Example 5 of DE-OS No. 28 15 926, the 4-(oxiranylmethoxy)-9H-carbazole of formula II is reacted with the secondary amine N-[2-(2'-(methoxy)-phenoxy)-ethyl]-benzylamine of formula V to yield the 1-[N-(benzyl)-2'-(2'-(methoxy)-phenoxy)-ethyl]-amino-3-[9H-carbazol-4"-yloxy]-propan-2-ol [benzyl-carvedilol] of the formula

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VIII

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which could be separated only after a purification step by column chromatography. This procedure is uneconomical for manufacturing on an industrial scale. The reaction of the compounds of the formulae II and V was carried out in ethylene glycol dimethyl ether.

[0007] Example 5 of DE-OS No. 28 15 926 was reproduced on a fourfold scale. As shown by Example for Comparison No. I, only a yield of 60% could be achieved, and a contaminated product was obtained which has a melting point of 92°C significantly lower than the value indicated in Example 5 of DE-OS No. 28 15 926 (97 to 99°C) and also lower than the values obtained in Examples 1 and 5 (93 to 95°C) and 2, 11 and 12 (94 to 98°C) of the present application. Without purification by column chromatography, it was failed to crystallize the product, thus, this purification procedure cannot be avoided. This is a considerable disadvantage in case of industrial application. Since the enlargement of scale of the above known process is accompanied by the reduction of both yield and quality of the product, said process is not suitable as an industrial one.

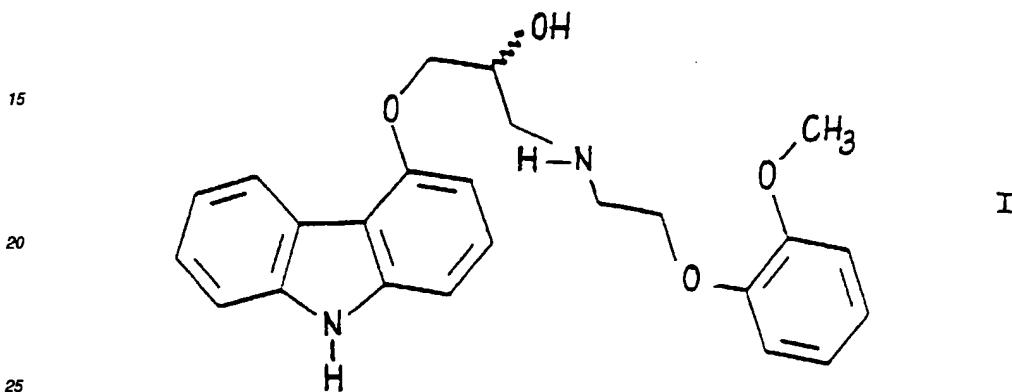
[0008] The process indicated in Example 5 of DE-OS No. 28 15 926 was modified by using, instead of ethylene glycol dimethyl ether, ethyl acetate or dioxan as shown by Examples for Comparison Nos. II and III. Even after a reaction

period of 28 hours, about half of the starting compound remained unreacted in dioxan, and practically no reaction has taken place in ethyl acetate.

[0009] The problem underlying to the invention is to provide for a new economical process and new intermediates for preparing 1-[9'H-carbazol-4'-yloxy]-3-[(2''-methoxy)phenoxy]-ethyl]-amino]-propan-2-ol [carvedilol] by which by overcoming the above disadvantages of the known processes and intermediates this compound can be obtained with high yields and in a simple way with drastically reduced formation of by-products and thus without the necessity of purification steps, which process also can be carried out on large scale industrially.

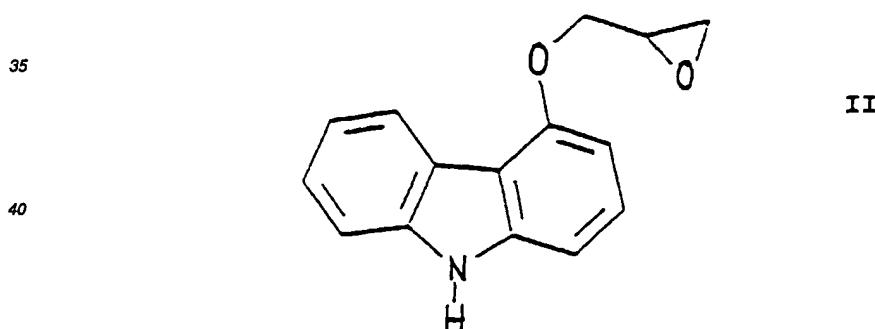
[0010] Surprisingly this has been achieved by the present invention.

[0011] A subject matter of the invention is a process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[(2''-(2''-methoxy)phenoxy)-ethyl]-amino]-propan-2-ol [carvedilol] of formula



as well as the optically active R or S enantiomer thereof and mixtures of the enantiomers and acid addition salts of these compounds which is characterized in that

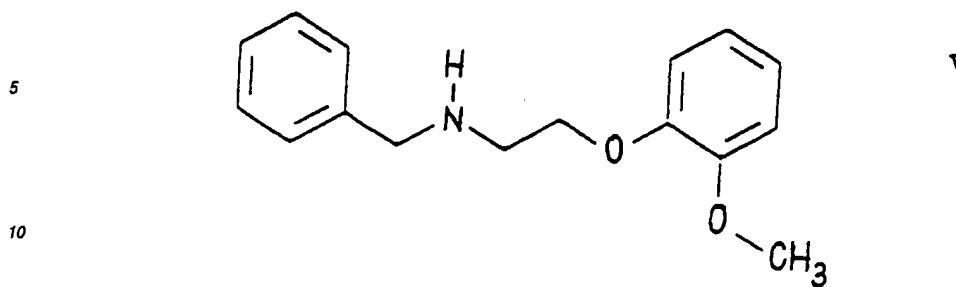
30 a) 4-(oxiranymethoxy)-9H-carbazole of formula



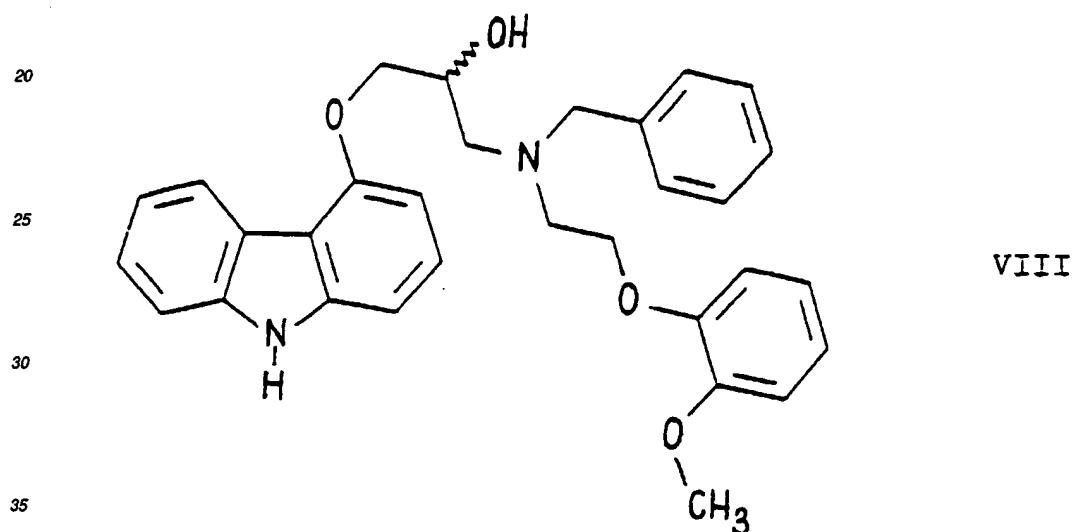
or the R or S enantiomer thereof is reacted with the secondary amine N-[2-(2'-methoxy)phenoxy]-ethyl]-benzylamine of formula

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15 in a protic organic solvent, and the thus formed 1-[N-[benzyl]-2'-(2'-methoxyphenoxy)-ethyl]-amino]-3-[9³H-carbazol-4"-yloxy]-propan-2-ol [benzyl-carvedilol] of formula



is debenzylated by catalytic hydrogenation or

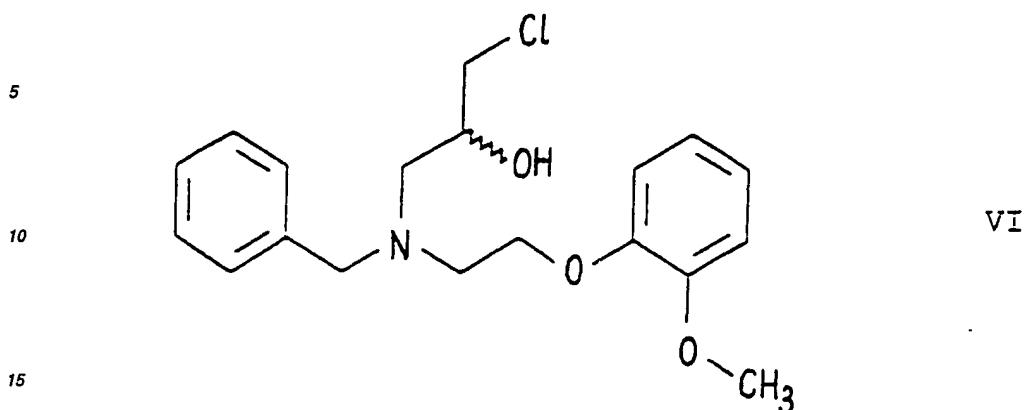
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b) the secondary amine N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine of formula V is reacted with epichlorohydrin in a manner known per se, the thus formed chloro compound 1-[N-[benzyl]-2'-(2'-methoxyphenoxy)-ethyl]-amino]-3-[chloro]propan-2-ol of formula

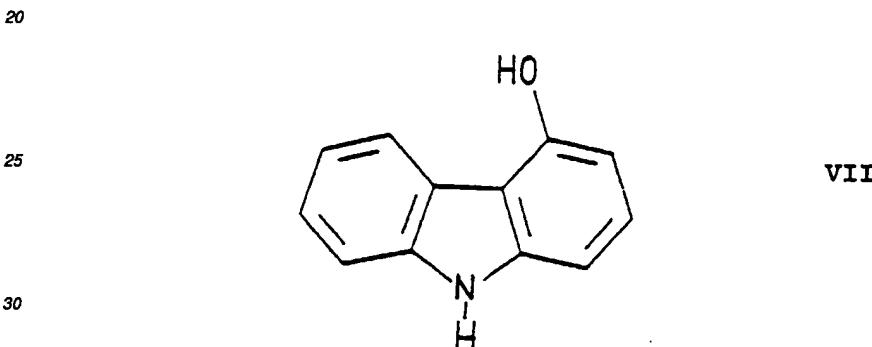
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is reacted with 4-(hydroxy)-9H-carbazole of formula



35 and the thus formed 1-[N-(benzyl)-2'-(2''-methoxyphenoxy)-ethyl]-amino]-3-[9H-carbazol-4''-yloxy]-propan-2-ol [benzyl-carvedilol] of formula VIII is debenzylated by catalytic hydrogenation

40 and, in a manner known per se, if desired, the 1-[9H-carbazol-4''-yloxy]-3-[2'-(2''-methoxyphenoxy)-ethyl]-amino]-propan-2-ol thus obtained is reacted with inorganic or organic acids to yield acid addition salts thereof or, if desired, liberating the free 1-[9H-carbazol-4''-yloxy]-3-[2'-(2''-methoxyphenoxy)-ethyl]-amino]-propan-2-ol base [carvedilol] of formula I from acid addition salts thereof and, if desired, converting the free 1-[9H-carbazol-4''-yloxy]-3-[2'-(2''-methoxyphenoxy)-ethyl]-amino]-propan-2-ol base [carvedilol] into other acid addition salts and/or, if desired, separating the enantiomers.

45 [0012] In variant a) of the process according to the invention the protic solvent is preferably 1 or more C₁₋₄ alkanol(s), particularly ethanol and/or isopropanol, most particularly the second one, and the reaction of the 4-(oxiranylmethoxy)-9H-carbazole of formula II with the secondary amine N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine of formula V is carried out advantageously at 0 bis 120°C, preferably at the boiling point of the reaction mixture.

50 [0013] Both in variant a) and variant b), the secondary amine N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine of formula V can be employed as an oil, i.e. in a form without crystal water, but preferably in a form containing crystal water.

55 [0014] In variant b) of the process according to the invention, the reaction of the secondary amine N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine of formula V with the epichlorohydrin is carried out in the absence or presence of a solvent, advantageously at a temperature of 0 to 150°C. The solvent can be an organic solvent of protic, dipolar aprotic or apolar character. It is preferred to perform the reaction in the absence of any solvent; in this case suitably an excess of epichlorohydrin is used and the reaction is carried out at a temperature of 30 to 80°C.

55 [0015] Suitably the chloro compound 1-[N-(benzyl)-2'-(2''-methoxyphenoxy)-ethyl]-amino]-3-[chloro]-propan-2-ol of formula VI is reacted with the 4-(hydroxy)-9H-carbazole of formula VII in an organic solvent of dipolar aprotic or apolar character at a temperature of 0 to 150°C. A preferred solvent is acetonitrile, and the reaction is performed suitably at the boiling point of the reaction mixture.

[0016] In both variant a) and variant b) of the process according to the invention, the formed 1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol [benzyl-carvedilol] of formula VIII is either separated and then debenzylated, or preferably it is not separated from the reaction mixture in which it was prepared before the debenzylation reaction. The debenzylation by catalytic hydrogenation can be carried out in a manner known per se in connection with the removal of a benzyl group.

5 [0017] Preferably as a catalyst palladium on carbon is used. The catalyst can be used several times, without regeneration procedure, for the debenzylation of the 1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol [benzyl-carvedilol] of formula VIII. Preferably the hydrogenation is carried out using hydrazine hydrate.

10 [0018] The optically active 1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol [benzyl-carvedilol] enantiomers of formula VIII i.e.

R-(+)-1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol
and
15 S-(-)-1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol

are novel compounds.

[0019] Hence a further subject matter of the present invention are the new compounds R-(+)-1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol and S-(-)-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol, and acid addition salts thereof, preferably the pharmaceutically acceptable ones, which are valuable intermediates via which the end product 1-[9⁹H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxy)phenoxy}-ethyl]-amino]-propan-2-ol [carvedilol] can be prepared by a process having originality in a superior way.

20 [0020] These intermediates can be prepared by stopping variants of the process according to the invention at the suitable stage.

[0021] The R and S enantiomers of the 4-(oxiranylmethoxy)-9H-carbazole of formula II usable as starting compounds can have been prepared by the process known from DE-OS No. 33 19 027. The secondary amine N-[2-(2'-methoxy)phenoxy]-ethyl]-benzylamine of formula V can have been prepared by the method of Augstein (J. Med. Chem., 8 [1965], 356 to 367) or in the manner given in the description.

30 [0022] 1-[9⁹H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxy)phenoxy}-ethyl]-amino]-propan-2-ol [carvedilol] of very high purity is produced in a yield of about 80% by the process of the invention. In the process no bis compound of formula IV forms.

[0023] Also the 1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol [benzyl-carvedilol] of formula VIII is obtained in a very pure state, and consequently no separation is required, and it can be 35 debenzylated in the reaction mixture in which it was formed.

[0024] On the basis of the above characteristics, the process of the invention can be carried out simply and economically.

[0025] An expert could not expect that, in variant a) of the process according to the invention, by using a protic organic solvent, the reaction of the 4-(oxiranylmethoxy)-9H-carbazole of formula II and the secondary amine N-[2-(2'-methoxy)phenoxy]-ethyl]-benzylamine of formula V gives, without special purification procedure, the 1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol [benzyl-carvedilol] of formula VIII in a well crystallizing and pure form and in a yield of near or above 90%, since, on the basis of the Examples for Comparison, with the opposite of it could be reckoned.

[0026] Also variant b) of the process according to the invention is surprising in that by it the side-reaction forming the 45 bis compound of formula IV is avoided. Thereby the product of suitable purity without purification by chromatography of the 1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol [benzyl-carvedilol] of formula VIII can be prepared in an economic way.

[0027] The invention is further elucidated by means of the following Examples.

50 Example 1

1-[N-[Benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-carbazol-4'-yloxy]-propan-2-ol

[0028] To 20 ml of ethanol 2.7 g (10.5 mmoles) of N-[2-(2'-methoxy)phenoxy]-ethyl]-benzylamine and 1.92 g (8.0 55 mmoles) of 4-(oxiranylmethoxy)-9H-carbazole are added, the reaction mixture is boiled for 5 hours under stirring, then allowed to cool, and stirred for further 16 hours at room temperature. The crystals are filtered, washed once with 10 ml of ethanol, once with 15 ml of diisopropyl ether, and dried under a lamp emitting infrared radiation.

[0029] Thus, 3.44 g (86.3%) of the title compound 1-[N-[benzyl]-2'-{[2'-methoxy]phenoxy}-ethyl]-amino]-3-[9⁹H-car-

bazol-4"-yloxy)-propan-2-ol are obtained in the form of white crystals. M.p.: 93 to 95°C.

Example 2

5 1-[N-(Benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[9H-carbazol-4"-yloxy]-propan-2-ol

[0030] To 25 ml of isopropanol 3.85 g (13.1 mmoles) of N-[2-(2'-methoxy)phenoxy-ethyl]-benzylamine and 2.4 g (10.0 mmoles) of 4-(oxiranylmethoxy)-9H-carbazole are added, the reaction mixture is boiled for 5 hours under stirring, then allowed to cool, and stirred for further 15 hours at room temperature. The crystals are filtered, washed once with 10 ml of isopropanol, twice with 2 ml of diisopropyl ether each time, and dried under a lamp emitting infrared radiation.

10 [0031] Thus, 4.8 g (96.3%) of the title compound 1-[N-(benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[9H-carbazol-4"-yloxy]-propan-2-ol are obtained in the form of white crystals. M.p.: 94 to 96°C.

Example 3

15 S-(*-*)-1-[N-(Benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[9H-carbazol-4"-yloxy]-propan-2-ol

[0032] To 25 ml of isopropanol 3.85 g (13.1 mmoles) of N-[2-(2'-methoxy)phenoxy-ethyl]-benzylamine and 2.4 g (10.0 mmoles) of S-(*-*)-4-(oxiranylmethoxy)-9H-carbazole are added, the reaction mixture is boiled for 7 hours under stirring, and the mixture is evaporated under reduced pressure. On standing, the evaporation residue crystallizes, the crystal mass is stirred with 12 ml of diethyl ether for half an hour, the crystals are filtered and washed twice using 10 ml of diethyl ether each time. The crude product is recrystallized from 40 ml of diisopropyl ether.

20 [0033] Thus, 3.52 g (70.6%) of the title compound S-(*-*)-1-[N-(benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[9H-carbazol-4"-yloxy]-propan-2-ol are obtained. M.p.: 102.5 to 103.5°C.

25 $[\alpha]_D = -9.6^\circ$ (20°C, c = 1, acetic acid)
 $[\alpha]_{435\text{ nm}} = 14.5^\circ$ (20°C, c = 1, acetic acid).

Example 4

30 R-(*+*)-1-[N-(Benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[9H-carbazol-4"-yloxy]-propan-2-ol

[0034] To 25 ml of isopropanol, 3.85 g (13.1 mmoles) of N-[2-(2'-methoxy)phenoxy-ethyl]-benzylamine and 2.4 g (10.0 mmoles) of R-(*+*)-4-(oxiranylmethoxy)-9H-carbazole are added, the reaction mixture is boiled for 7 hours under stirring, and the mixture is evaporated under reduced pressure. The evaporation residue is crystallized from diisopropyl ether, and the crystals are filtered. The crude product is suspended in 50 ml of diisopropyl ether, the suspension is heated to boiling, then cooled and filtered.

35 [0035] Thus, 4.09 g (82.1% of the title compound R-(*+*)-1-[N-(benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[9H-carbazol-4"-yloxy]-propan-2-ol are obtained. M.p.: 103 to 104°C.

40 $[\alpha]_D = +8.2^\circ$ (20°C, c = 1, acetic acid).
 $[\alpha]_{435\text{ nm}} = +12.4^\circ$ (20°C, c = 1, acetic acid).

Example 5

45 [0036]

a) 1-[N-(Benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[chloro]-propan-2-ol
50 10.3 g (40 mmoles) of N-[2-(2'-methoxy)phenoxy-ethyl]-benzylamine are dissolved in 16 ml of epichlorohydrin, and the solution obtained is stirred at 55 to 60°C for 3 hours. The reaction mixture is evaporated under reduced pressure, 20 ml of toluene are added, evaporated and the procedure is repeated.

Thus, 13.8 g (99%) of the title compound 1-[N-(benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[chloro]-propan-2-ol are obtained as an oily evaporation residue.

55 b) 1-[N-(Benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[9H-carbazol-4"-yloxy]-propan-2-ol
3.5 g (10 mmoles) of 1-[N-(benzyl)-2'-(2'-methoxy)phenoxy-ethyl]-amino]-3-[chloro]-propan-2-ol, prepared as described under a), and 0.92 g (5 mmoles) of 4-(hydroxy)-9H-carbazole are dissolved in 25 ml of dioxan. To the solution obtained, 0.69 g (5.0 mmoles) of potassiumcarbonate are added, and the reaction mixture is boiled for 28

hours under stirring, then cooled to 25°C. The inorganic salt is filtered off, washed with dioxan and the filtrate is evaporated under reduced pressure. To the 4.6 g of evaporation residue 25 ml of isopropanol are added. The mixture is heated to 60°C, and allowed to cool under stirring. After 24 hours the crystals are filtered off and washed with diisopropyl ether.

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[0037] Thus, 1.79 g (71.7%) of the title compound 1-[N-(benzyl)-2'-(2"-methoxy)phenoxy]-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol are obtained in the form of white crystals. M.p.: 93 to 95°C.

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Example 6

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1-[9'H-carbazol-4'-yloxy]-3-[2'-(2"-methoxy)phenoxy]-ethyl]-amino]-propan-2-ol

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[0038] To 100 ml of ethanol 15.4 g (52.5 mmoles) of N-[2-(2'-methoxy)phenoxy]-ethyl]-benzylamine containing 2 molecules of crystal water, prepared as described in Example 1, 3 or 5, and 9.6 g (40.0 mmoles) of 4-(oxiranyl)-methoxy)-9H-carbazole are added, and the suspension is heated to boiling. The solution obtained is boiled for 5 hours under stirring, then cooled to room temperature, and 10.4 g of wet palladium on carbon catalyst are added. (The catalyst has a water content of 50.6% by weight and contains 16.2% by weight of palladium calculated on the dry catalyst). To the mixture cooled with cold water 40 ml (0.806 moles) of 98% by weight hydrazine hydrate are added, drop by drop, at 15 to 30°C in 15 minutes, and the reaction mixture is stirred at 25°C for 18 hours. Then, the catalyst is filtered off, washed three times using 100 ml of ethanol each time, and the filtrate is evaporated under reduced pressure. To the evaporation residue 200 ml of water and 200 ml of 1,2-dichloroethane are added, the mixture is stirred until the evaporation residue is dissolved, the phases are separated, and the aqueous phase is still twice extracted using 150 ml of 1,2-dichloroethane each time. The organic phase is dried, then evaporated under reduced pressure. The evaporation residue is heated to boiling with 40 ml of ethyl acetate, the hot mixture is filtered through a folded paper filter while hot, and the filtrate is allowed to cool under stirring. After the precipitation of the crystals, the mixture is stirred for a further hour at 25°C, the crystals are filtered off and washed three times using 10 ml of cold ethyl acetate each time. The product is dried under a lamp emitting infrared radiation.

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[0039] Thus, 13.05 g (80.0%) of crude product are obtained as white crystals. M.p.: 113 to 116°C. The crude product is recrystallized from 75 ml of ethyl acetate yielding 12.1 g (74.2%) of the title compound 1-[9'H-carbazol-4'-yloxy]-3-[2'-(2"-methoxy)phenoxy]-ethyl]-amino]-propan-2-ol. M.p.: 114 to 116°C.

30

Example 7

35

1-[9'H-Carbazol-4'-yloxy]-3-[2'-(2"-methoxy)phenoxy]-ethyl]-amino]-propan-2-ol

40

[0040] Into a flask of 100 ml capacity 1.99 g (4 mmoles) of 1-[N-(benzyl)-2'-(2"-methoxy)phenoxy]-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol, prepared as described in Example 1, 3 or 5, 40 ml of ethanol, 4 ml of water and 1.0 g of wet palladium on carbon catalyst having a water content of 50.6% by weight and containing 16.2% by weight of palladium calculated on the dry catalyst are added. To the mixture cooled with cold water, 4 ml (80 mmoles) of 98% by weight hydrazine hydrate are added, drop by drop, at 5 to 10°C in 10 minutes, and the reaction mixture is stirred at 25°C for 2 hours. The catalyst is filtered off, washed twice using 20 ml of ethanol each time, and the filtrate is evaporated under reduced pressure. To the evaporation residue 50 ml of water and 50 ml of 1,2-dichloroethane are added, the mixture is stirred until dissolution, then the phases are separated, and the aqueous phase is further extracted twice using 50 ml of 1,2-dichloroethane each time. The organic phase is dried and evaporated under reduced pressure. The evaporation residue is heated to boiling with 9 ml of ethyl acetate, filtered through a folded paper filter, while hot, and the filtrate is allowed to cool under stirring. After the precipitation of the crystals, the mixture is stirred at 25°C for a further hour, the crystals are filtered off, and washed twice using 1 ml of cold ethyl acetate each time. The product is dried under a lamp emitting infrared radiation.

45

[0041] Thus, 1.33 g (81.6%) of the title compound 1-[9'H-carbazol-4'-yloxy]-3-[2'-(2"-methoxy)phenoxy]-ethyl]-amino]-propan-2-ol are obtained as white crystals. M.p.: 114 to 116°C.

50

Example 8

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1-[9'H-Carbazol-4'-yloxy]-3-[2'-(2"-methoxy)phenoxy]-ethyl]-amino]-propan-2-ol

60

[0042] To 60 ml of ethanol, 1.1 g (2.2 mmoles) of 1-[N-(benzyl)-2'-(2"-methoxy)phenoxy]-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol, prepared as described in Example 1, 3 or 5, and 0.5 g of wet palladium on carbon catalyst having a water content of 50.6% by weight and containing 16.2% by weight of palladium calculated on the dry catalyst

are added. The mixture is vigorously stirred under a hydrogen atmosphere of 5 bar at room temperature. The reduction is finished in about 3 hours. The catalyst is filtered off, washed twice with ethanol using 20 ml of ethanol each time, and the filtrate is evaporated under reduced pressure. To the evaporation residue, 5 ml of ethyl acetate are added, the mixture is stirred at 25°C for 2 hours, the crystals obtained are filtered off, washed twice using 1 ml of cold ethyl acetate each time. The product is dried under a lamp emitting infrared radiation.

[0043] Thus, 0.69 g (76.6%) of the title compound 1-[9'H-carbazol-4'-yloxy]-3-[(2"-{methoxy}phenoxy)-ethyl]-amino]-propan-2-ol are obtained as white crystals. M.p.: 114 to 116°C.

Example 9

R-(+)-1-[9'H-Carbazol-4'-yloxy]-3-[(2"-{methoxy}phenoxy)-ethyl]-amino]-propan-2-ol

[0044] To 40 ml of ethanol, 1.99 g (4 mmoles) of R-(+)-1-[N-{benzyl}-2'-(2"-{methoxy}phenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol, prepared as described in Example 4, and 1.0 g of wet palladium on carbon catalyst having a water content of 50.6% by weight and containing 16.2% by weight of palladium calculated on the dry catalyst are added. To the mixture 4 ml (80 mmoles) of 98% by weight hydrazine hydrate are added, drop by drop, at 20 to 30°C in 20 minutes, and the reaction mixture is stirred at 25°C for 1.5 hours. The catalyst is filtered off, washed twice with ethanol using 30 ml of ethanol each time, and the filtrate is evaporated under reduced pressure. To the evaporation residue, 80 ml of water and 80 ml of 1,2-dichloromethane are added, the mixture is stirred until the evaporation residue is dissolved, then the phases are separated, and the aqueous phase is extracted still twice using 80 ml of 1,2-dichloromethane each time. The organic phase is dried, then evaporated under reduced pressure. The evaporation residue is heated to boiling with 5 ml of ethyl acetate, the mixture is filtered, while hot, through a folded paper filter, and the filtrate is allowed to cool under stirring. After the precipitation of the crystals, the mixture is stirred at 25°C for further 8 hours, the crystals are filtered off, and washed twice using 3 ml of cold ethyl acetate each time. The crude product is recrystallized from 8 ml of ethyl acetate.

[0045] Thus, 1.16 g (71.2%) of the title compound R-(+)-1-[9'H-carbazol-4'-yloxy]-3-[(2"-{methoxy}phenoxy)-ethyl]-amino]-propan-2-ol are obtained as white crystals. M.p.: 112 to 113°C. $[\alpha]_D = +17.2^\circ$ (20°C, c = 1, acetic acid).

Example 10

S-(+)-1-[9'H-Carbazol-4'-yloxy]-3-[(2"-{methoxy}phenoxy)-ethyl]-amino]-propan-2-ol

[0046] To 35 ml of ethanol, 1.74 g (3.5 mmoles) of S-(+)-1-[N-{benzyl}-2'-(2"-{methoxy}phenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol, prepared as described in Example 3, and 0.9 g of wet palladium on carbon catalyst having a water content of 50.6% by weight and containing 16.2% by weight of palladium calculated on the dry catalyst are added. To the mixture 3.5 ml (70 mmoles) of 98% by weight hydrazine hydrate are added, drop by drop, at 20 to 30°C in 10 minutes, and the reaction mixture is stirred at 25°C for 1.5 hours. The catalyst is filtered off, washed twice with ethanol using 30 ml of ethanol each time, and the filtrate is evaporated under reduced pressure. To the evaporation residue, 70 ml of water and 70 ml of 1,2-dichloromethane are added, the mixture is stirred until the evaporation residue is dissolved, then the phases are separated, and the aqueous phase is still twice extracted using 70 ml of dichloromethane each time. The organic phase is dried, then evaporated under reduced pressure. The evaporation residue is heated to boiling with 5 ml of ethyl acetate, the mixture is filtered, while hot, through a folded paper filter, and the filtrate is allowed to cool under stirring. After the precipitation of the crystals, the mixture is stirred at 25°C for further 2 hours, the crystals are filtered off, and washed twice using 2 ml of cold ethyl acetate each time. The crude product is recrystallized from 7.5 ml of ethyl acetate.

[0047] Thus, 1.15 g (80.7%) of the title compound S-(+)-1-[9'H-carbazol-4'-yloxy]-3-[(2"-{methoxy}phenoxy)-ethyl]-amino]-propan-2-ol are obtained as white crystals. M.p.: 110 to 111.5°C.

$[\alpha]_D = +18.1^\circ$ (20°C, c = 1, acetic acid).

Example 11

1-[N-{Benzyl}-2'-(2"-{methoxy}phenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol

[0048] 41.2 g (160 mmoles) of N-[2-(2'-{methoxy}phenoxy)-ethyl]-benzylamine are dissolved in 64 ml of epichlorohydrin, and the solution obtained is stirred at 55 to 60°C for 3.5 hours. Then, the reaction mixture is evaporated under reduced pressure, to the residue 20 ml of toluene are added, evaporated, and this procedure is repeated once more. To the 56.0 g of oily evaporation residue 300 ml of acetonitrile and 14.66 g (80 mmoles) of 4-(hydroxy)-9H-carbazole

are added. To the solution obtained 13.45 g (160 mmoles) of sodium hydrogen carbonate are added, and the reaction mixture is stirred under boiling for 20 hours. The mixture is cooled to 25°C, the inorganic salt is filtered off, washed with acetonitrile. The filtrate is evaporated under reduced pressure. To the 68.6 g of evaporation residue, 160 ml of isopropanol are added. The mixture is heated to 60°C, and allowed to cool under stirring. In 3 hours a thick suspension is obtained which is cooled with ice-water, filtered, and washed with 100 ml of cold isopropanol and 100 ml of diisopropyl ether. The product is dried under a lamp emitting infrared radiation.

5 [0049] Thus, 31.80 g (80.0%) of the title compound 1-[N-{benzyl}-2'-(2'-methoxyphenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol are obtained as white crystals. M.p.: 94 to 96°C.

10 Example 12

1-[N-{Benzyl}-2'-(2'-methoxyphenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol

15 [0050] To 2 450 ml of isopropanol 385 g of N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine dihydrate and 240 g of 4-(oxiranylmethoxy)-9H-carbazole are added, the reaction mixture is boiled under stirring for 6 hours, allowed to cool, and stirred at room temperature for further 16 hours. The crystalline product is filtered off, washed with 400 ml of isopropanol, then twice with diisopropyl ether using 200 ml of diisopropyl ether each time, and dried.

20 [0051] Thus, 469 g (94%) of the title compound 1-[N-{benzyl}-2'-(2'-methoxyphenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol are obtained as white crystals. M.p.: 94 to 96°C.

20 [0052] Preparation of the starting compound:

Preparation of N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine of formula V

25 [0053]

25 N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine dihydrate

30 [0054] To 131 ml (128.64 g, 1.2 moles) of benzylamine heated to 80°C 69.33 g (0.3 moles) of 1-[2'-(bromo)ethoxy]-2-[methoxy]benzene are added in 25 minutes. The rate of addition is adjusted to maintain the inner temperature of the reaction mixture at 95 to 105°C. After the addition, the mixture is stirred at an inner temperature of 95 to 100°C for 2 hours, the suspension obtained is cooled in ice-water to 25°C, then poured into 1 000 ml of 10% by weight hydrochloric acid cooled with ice-water in 5 minutes taking care that the inner temperature should not exceed 50°C. The solution obtained is cooled with ice-water. In 5 to 10 minutes, the hydrochloride of the product precipitates in the form of crystals. The crystal suspension is stirred at 5 to 10°C for half an hour, filtered, washed with water. The crude hydrochloride is recrystallized from 400 ml of water, filtered and washed with water.

35 [0055] Thus, 71.9 g (81.6%) of the hydrochloride of the title compound N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine dihydrate are obtained. M.p.: 148 to 150°C.

40 [0056] The hydrochloride is suspended in 300 ml of water, the suspension is heated until the crystals dissolve, and, to the warm solution, 100 ml of 10% by weight aqueous sodium hydroxide solution are added, drop by drop. The solution is cooled with ice-water to a temperature of 5 to 10°C, the crystals are filtered, washed with 100 ml of cold water and dried on the air at room temperature.

45 [0057] Thus, 43.1 g (48.9%) of the title compound N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine dihydrate are obtained. The product contains crystal water ($C_{16}H_{19}NO_2 \cdot 2H_2O$). M.p.: 53 to 55°C.

45 Example for Comparison No. I

(Reproduction of Example 5 of DE-OS No. 28 15 926)

50 [0058] A mixture of 60.4 g of 4-(oxiranylmethoxy)-9H-carbazole, 64.8 g of N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine and 200 ml of ethylene glycol dimethyl ether was boiled for 24 hours. On cooling the mixture, the product did not precipitate. The mixture was evaporated under reduced pressure, the residual oil could not be crystallized from ethanol, isopropanol and acetone, wherefore it was transferred to a column filled with silica gel. In the column chromatography 1,2-dichloromethane, a mixture containing 9 volumes of 1,2-dichloroethane and 1 volume of ethyl acetate, a mixture containing 7 volumes of 1,2-dichloroethane and 3 volumes of ethyl acetate, and, at last, ethyl acetate were used as the solvent. The fractions containing the product were combined and evaporated to yield 75 g (60%) of 1-[N-{benzyl}-2'-(2'-methoxyphenoxy)-ethyl]-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol (benzyl-carvedilol) M.p.: 92°C.

Example for Comparison No. II

[0059] A mixture of 1.92 g (8 mmoles) of 4-(oxiranylmethoxy)-9H-carbazole, 3.08 g (10.5 mmoles) of N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine and 20 ml of ethyl acetate was boiled. The reaction was followed by means of HPLC.

5 After 28 hours, the reaction mixture contained merely 3% by weight of 1-[N-(benzyl)-2'-(2'-methoxyphenoxy)-ethyl]-amino]-3-[9H-carbazol-4'-yloxy]-propan-2-ol [benzyl-carvedilol], practically the whole amount of the starting 4-(oxiranylmethoxy)-9H-carbazole remained unreacted. The characteristics of HPLC:

Column: LiChrospher 100RP-18 (5 μ m), λ = 254 nm.

10 Acetonitrile: buffer solution = 1 : 1

flow velocity: 0.5 ml/min.

Buffer solution: 7.74 g of ammonium acetate and 10.5 ml of acetic acid in 1 000 ml of aqueous solution.

Retention times:

15

[0060]

20

N-[2-(2'-methoxyphenoxy)-ethyl]-benzylamine	2.0 min.
4-(oxiranylmethoxy)-9H-carbazole	4.6 min.
1-[N-(benzyl)-2'-(2'-methoxyphenoxy)-ethyl]-amino]-3-[9H-carbazol-4'-yloxy]-propan-2-ol [benzyl-carvedilol]	14.1 min.

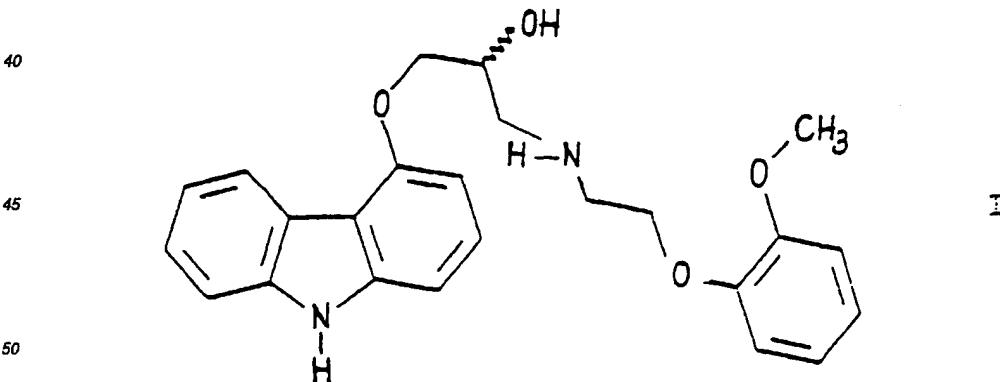
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Example for Comparison No. III

[0061] The procedure of Example for Comparison No. II was repeated with the difference that 20 ml of dioxane were 30 used as the solvent. After 28 hours of reaction, about 50% by weight of the amount of the starting 4-(oxiranylmethoxy)-9H-carbazole was still present as determined by HPLC.

Claims

35 1. A process for preparing 1-[9H-carbazol-4'-yloxy]-3-[2'-(2'-methoxyphenoxy)-ethyl]-amino]-propan-2-ol [carvedilol] of formula



as well as the optically active R or S enantiomer thereof and mixtures of the enantiomers and acid addition salts of these compounds, characterized in that

55 a) 4-(oxiranylmethoxy)-9H-carbazole of formula



15

or the R or S enantiomer thereof is reacted with the secondary amine N-[2-(2'-methoxy)phenoxy]-ethyl]-benzylamine of formula



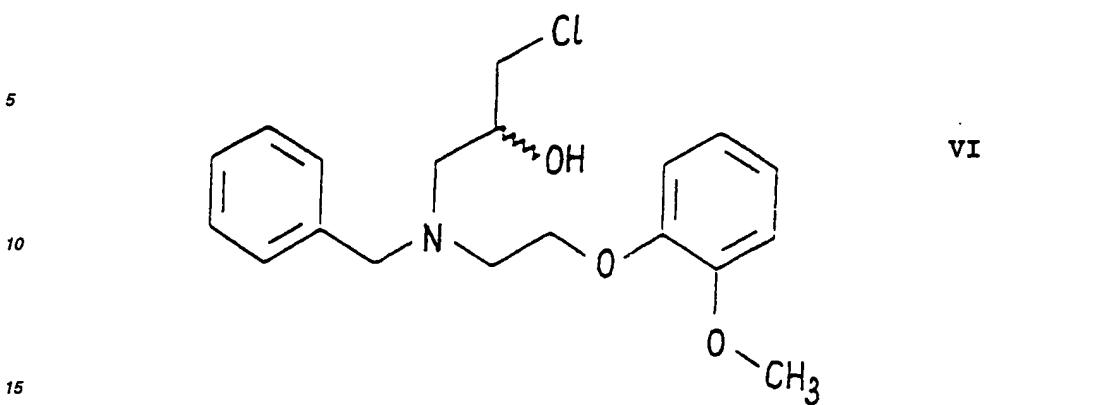
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in a protic organic solvent, and the thus formed 1-[N-(benzyl)-2'-({2"-methoxy}phenoxy)-ethyl]-amino]-3-[9'"H-carbazol-4"-yloxy]-propan-2-ol [benzyl-carvedilol] of formula

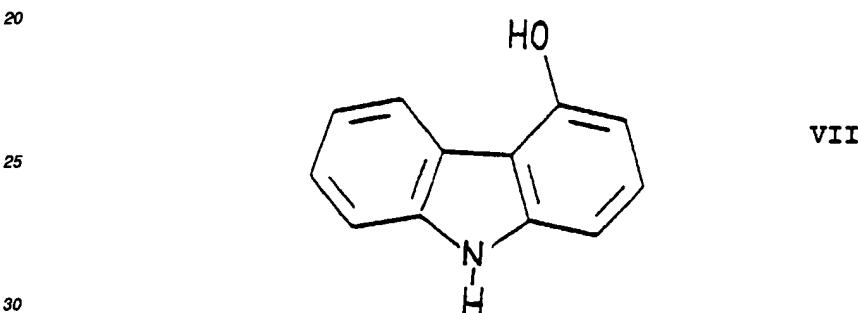


is debenzylated by catalytic hydrogenation or

55 b) the secondary amine N -[2-(2'-methoxy)phenoxy]-ethylbenzylamine of formula V is reacted with epichlorohydrin in a manner known per se, the thus formed chloro compound 1-[N-(benzyl)2'-(2'-methoxy)phenoxy]-ethyl-amino]-3-[chloro]propan-2-ol of formula



is reacted with 4-(hydroxy)-9H-carbazole of formula



35

and the thus formed 1-[N-[benzyl]-2'-({2"-methoxy-phenoxyl}-ethyl)-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol [benzyl-carvedilol] of formula VIII is debenzylated by catalytic hydrogenation and, in a manner known per se, if desired, the 1-[9'H-carbazol-4'-yloxy]-3-[{2"-({2"-methoxy-phenoxyl}-ethyl)-amino}-propan-2-ol thus obtained is reacted with inorganic or organic acids to yield acid addition salts thereof or, if desired, liberating the free 1-[9'H-carbazol-4'-yloxy]-3-[{2"-({2"-methoxy-phenoxyl}-ethyl)-amino}-propan-2-ol base [carvedilol] of formula I from acid addition salts thereof and, if desired, converting the free 1-[9'H-carbazol-4'-yloxy]-3-[{2"-({2"-methoxy-phenoxyl}-ethyl)-amino}-propan-2-ol base [carvedilol] into other acid addition salts and/or, if desired, separating the enantiomers.

40

2. A process according to claim 1, characterized in that the 1-[N-[benzyl]-2'-({2"-methoxy-phenoxyl}-ethyl)-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol [benzyl-carvedilol] of formula VIII is not separated from the reaction mixture in which it was prepared before the debenzylation reaction.

45

3. R-(+)-1-[N-[benzyl]-2'-({2"-methoxy-phenoxyl}-ethyl)-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol and acid addition salts thereof.
4. S-(-)-1-[N-[benzyl]-2'-({2"-methoxy-phenoxyl}-ethyl)-amino]-3-[9'H-carbazol-4"-yloxy]-propan-2-ol and acid addition salts thereof.



European Patent
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EUROPEAN SEARCH REPORT

Application Number

EP 98 12 2114

DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)						
D, X	DE 28 15 926 A (BOEHRINGER MANNHEIM GMBH) 18 October 1979 * example 5 *	1	C07D209/88						
D, A	DE 33 19 027 A (BOEHRINGER MANNHEIM GMBH) 29 November 1984 * claims *	1							
TECHNICAL FIELDS SEARCHED (Int.Cl.6)									
C07D									
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 33%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>17 February 1999</td> <td>Van Bijlen, H</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	17 February 1999	Van Bijlen, H
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<p>CATEGORY OF CITED DOCUMENTS</p> <table border="0" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top;"> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document </td> <td style="width: 50%; vertical-align: top;"> T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document </td> </tr> </table>				X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document	T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document				
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EP 98 12 2114

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17-02-1999

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 2815926	A	18-10-1979	AT 375639 B AU 522975 B AU 4582079 A BG 61419 B CA 1129416 A CS 227007 B CS 9104200 A CS 227047 B DD 143607 A DK 141979 A, B, EP 0004920 A FI 791142 A, B, HK 2385 A JP 1023462 B JP 1545837 C JP 54157558 A JP 63258416 A LT 2628 R LU 88320 A LV 5234 A MX 9203380 A US 4503067 A ZA 7901732 A	27-08-1984 08-07-1982 18-10-1979 31-07-1997 10-08-1982 16-04-1984 15-04-1992 16-04-1984 03-09-1980 14-10-1979 31-10-1979 14-10-1979 18-01-1985 02-05-1989 28-02-1990 12-12-1979 25-10-1988 25-04-1994 04-05-1994 10-10-1993 01-09-1992 05-03-1985 28-05-1980
DE 3319027	A	29-11-1984	AT 27273 T AU 551116 B AU 2848084 A CA 1259071 A CA 1257279 C DK 91393 A DK 255184 A EP 0127099 A FI 842046 A, B, GR 81577 A IE 57533 B JP 1818634 C JP 5027622 B JP 59222473 A JP 1917129 C JP 5208957 A JP 6013508 B PT 78633 B US 4824963 A US 4985454 A US 4697022 A US 5071868 A	15-06-1987 17-04-1986 29-11-1984 05-09-1989 11-07-1989 06-08-1993 27-11-1984 05-12-1984 27-11-1984 11-12-1984 24-03-1993 27-01-1994 21-04-1993 14-12-1984 23-03-1995 20-08-1993 23-02-1994 18-06-1986 25-04-1989 15-01-1991 29-09-1987 10-12-1991